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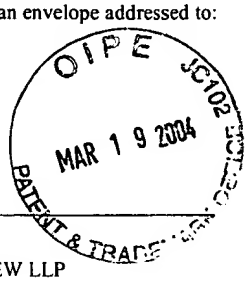

TOWNSEND and TOWNSEND and CREW LLP

By: Karen Karlin

PATENT
Attorney Docket No.: 018512-006510US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

CREECH et al.

Application No.: 09/927,267

Filed: August 10, 2001

For: CNG2B: A NOVEL HUMAN CYCLIC NUCLEOTIDE-GATED ION CHANNEL

Customer No.: 20350

Confirmation No. 6230

Examiner: Li, Ruixiang

Technology Center/Art Unit: 1646

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. ZHIXIN LIN

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, ZHIXIN LIN, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received my Ph.D.in the field of Molecular and Cell Biology from Brown University in 1996. Currently I am Program Scientist at ICAgen, Inc. I have been at this position and related positions for three and one-half years. A copy of my curriculum vitae is attached hereto as Exhibit A.

3. The invention of the above-referenced patent application provides for the first time a nucleic acid encoding human CNG2B, a member of the CNG family of cyclic nucleotide gated cation channels that is expressed primarily in the central nervous system (CNS).

4. I have read and am familiar with the contents of this patent application. In addition, I have read the Final Office Action, mailed September 16, 2003, received in the present case. It is my understanding that the Examiner does not believe that the present invention is supported by a specific, substantial, and credible asserted utility or a well established utility as required by the United States Patent Laws.

5. This declaration is provided to demonstrate that the identification of the coding sequence for CNG2B has a specific and substantial utility that is credible to one of ordinary skill in the art.

6. Rat OCNC2 encodes a polypeptide that is specifically expressed in the brain and capable of forming homomultimeric and, with OCNC1 alpha subunits, heteromultimeric cyclic nucleotide gated cation channels involved in olfactory signal transduction (Bradley *et al.*, *Proc. Natl. Acad. Sci. USA*, **91**:8890-8894, 1994, which was disclosed as Reference A in the Information Disclosure Statement filed June 11, 2002). Human CNG2B polypeptide is also highly expressed in the brain, and its amino acid sequence is more than 93% identical to that of rat OCNC2 (Figure 1 of the present application and Bradley *et al.*). This high level of sequence identity makes CNG2B the most homologous to rat OCNC2 among all known members of the human CNG family.

7. Given such a high level of amino acid sequence homology, one of ordinary skill in the art would believe that the novel human CNG2B gene is the ortholog of rat

OCNC2 gene. In other words, a skilled artisan would believe that human CNG2B and rat OCNC2 polypeptides have the same physiological function in mediating olfactory transduction.

8. Because of the involvement of CNG2B in olfactory transduction, one of ordinary skill in the art would recognize CNG2B as a therapeutic target for treating neurological disorders caused by olfactory sensory anomaly. The identification of human CNG2B coding sequence makes it possible to screen for activators and inhibitors of the CNG2B cation channel, which may be useful for, *e.g.*, treating neurological disorders related to altered olfactory sensory signal transduction. The present invention therefore has a specific and real-world use.

9. It is well known in the art that once an ion channel has been identified, modulators of this ion channel can be routinely identified based on the coding sequence of the ion channel and a method for activation of the channel. The present application provides nucleic acid sequences encoding human CNG2B polypeptides as well as methods for activating a CNG2B cation channel, one of ordinary skill in the art can thus conduct routine testing to identify activators or inhibitors of a CNG2B cation channel useful for modulating olfactory transduction in neuronal cells and for controlling neurological disorders related to abnormal olfactory transduction.

10. There are known instances where modulation of an ion channel is useful for treating a specific disease even though the channel itself may not cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure is useful and effective, even if the original cause of the hypertension is unrelated to vascular tone. Similarly, it is perfectly reasonable to expect that the targeting of a CNG2B channel, a cyclic nucleotide gated cation channel widely expressed in the CNS and involved in olfactory transduction, is an appropriate strategy for treating neurological disorders related to abnormal olfactory

transduction, whether or not such abnormality is directly caused by altered CNG2B activity. Thus, the disclosure of the present application is sufficient to establish the utility of CNG2B.

11. In summary, it is my scientific opinion that one of skill in the art, at the time the application was filed, would believe the physiological role human CNG2B plays in olfactory transduction and recognize the specific and real-world utility of the CNG2B encoding nucleic acids of the present invention.

Date March 10, 2004

By: _____
Zhixin Lin, Ph.D.

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachment (Exhibit A: Dr. Lin's CV)
CG/cg
60101717 v1

Zhixin Lin

109 Timber Hitch Rd.
Cary, NC 27513
(919) 462-5886
zlin@icagen.com

Icagen, Inc.
4222 Emperor Blvd. Suite 460
Durham, NC 27703
(919) 941-5206 ext. 613 (Office)
(919) 941-0813 (Fax)

EDUCATION

Ph.D. Molecular, Cell Biology and Biochemistry, *Brown University*, 1996
Sc.M. Chemistry, *Nankai University*, China, 1986
Sc.B. Chemistry, *Nankai University*, China, 1983

WORK EXPERIENCE

Icagen, Inc., Research Triangle Park. NC.
Program Scientist, September 2003-present
Coordinator of Molecular Biology Group
- Responsible for coordinating all the aspects of molecular biology on drug discovery programs in the area of glaucoma, inflammation and neuropathic pain using ion channel as targets
- Directly supervised a team of scientists for implementation of cloning and charaterization of novel genes, profiling gene expression of ion channels in human tissues and developing functional assays to validate drug targets

Icagen, Inc., Research Triangle Park. NC.
Senior Scientist, Department of Biology, Molecular Group September 2000-August 2003

Cold Spring Harbor Laboratory, Cold Spring Harbor. NY.
Postdoctoral Fellow, with Dr. Jerry Yin August 1997 – September 2000
Molecular mechanism of learning and memory
- Evaluating the tetracycline inducible system in cortical neurons and in transgenic mice.
- Investigating regulation of PKM-zeta on the expression of CREB in hippocampal and cortical neurons.

Brown University, Providence, RI.
Postdoctoral Fellow, with Dr. Diane Lipscombe May 1996 – July 1997
Structural determination of the N-type Ca channel isoforms
- Performed site-directed mutagenesis on splicing sites of the isoforms
- Investigated structural determination of the sites corresponding to the differences for channel gating and drug binding

Modulation of the N-type Ca channel
- Studied regulation of the N-type channel by protein kinase C
- Studied modulation of the N-type channel by G-proteins

Brown University, Providence, RI.
Graduate student, With Dr. Edward Hawrot September 1991 – May 1996
Identification of functionally distinct voltage-gated Ca channels in rat sympathetic neurons and brain
- Cloned full-length N-type Ca channel α_1 subunits from rat sympathetic neurons
- Identified multiple splicing sites in N-type Ca channel gene
- Constructed several high efficiency N-type isoform clones functionally expressing in *Xenopus* oocytes
- Identified functionally distinct isoforms of the N-type Ca channel in rat central and peripheral neurons

University of Delaware, Newark, DE.
Graduate student 1989 - 1990

Reactivity of paramagnetic chromium alkyls

- Performed Organometallic synthesis to study the reactivity of chromium alkyls with aldehydes

Drug Discovery Group, University of Georgia, Athens, GA.
Visiting scientist 1988 - 1989

Synthesis of antiviral AIDS agents and antineoplaston agents

- Designed and synthesized 2',3'- dideoxy nucleosides drugs
- Synthesized phenyl substituted analogues of 3-[N-phenylacetylaminopiperidine]-2,6,-dion

Nankai University, Tianjin, P. R. China
Graduate Student 1983 - 1986

Used Schwartz reagent to do hydrozirconation of nitriles

PUBLICATIONS

- Chu, D., Ullas, G.V., Jeong, H.K., Ahn, S.K., **Lin, Z.** and Beach, J.W. (1990). Synthesis and structure-activity relationships of 6-substituted 2',3'-virus agents. J. Med. Chem. **33**, 1553-1560.

- Chu, D., Huang, H.Q. and **Lin, Z.** (1990). Synthesis of phenyl substituted analogues of 3-[N-phenylacetylamino-piperidine]-2,6,-dion and their biological activities. J. Med. Chem. **35,** 157-161.

- Nairn, A.C., Talvinder, S.S., Andjus, P., Craig, A.M., Miyawaki, A., Kloppenburg, P., **Lin, Z.** and Pouzat, C. (1995). Rapid purification of protein phosphatase-2B (Calcineurin) from rat forebrain. Neuroprotocols **6**, 105-107.

- Talvinder, S.S., Nairn, A.C., Kloppenburg, P., **Lin, Z.** and Pouzat, C. (1995). A role for calcineurin (protein phosphatase-2B) in the regulation of glutamate release. Biochem. Biophys. Res. Comm. **212**, 609-616.

- **Lin, Z.**, Harris, C. and Lipscombe, D. (1996). The molecular identity of Ca channel α_1-subunits expressed in rat sympathetic neurons. J. Mol. Neurosci. **7**, 257-267.

- **Lin, Z.**, Haus, S., Edgerton, J. and Lipscombe, D. (1997). Identification of functionally distinct isoforms of the N-type Ca^{2+} channel in rat sympathetic ganglia and brain. Neuron **18**, 153-166.

- **Lin, Z.**, Lin, Y. and Lipscombe, D. (1997). Alternative splicing in the fourth domain of the Ca channel α_{1B}-subunit can account for the expression of kinetically distinct variants of the N-type Ca channel in the nervous system of the rat. J. Physiol. (Lond) **504**, 156.

- **Lin, Z.**, Lin Y., Schorge, S., Pan, J. Q., Beierlein, M. and Lipscombe, D. (1999). Alternative splicing of a short cassette exon in α_{1B} generates functionally distinct n-type calcium channels in central and peripheral neurons. J. Neurosci. **19**, 5322-5331.

- Schorge, S., Gupta, S., **Lin, Z.**, McEnery, M. W. and Lipscombe, D. (1999). Calcium channel activation stabilizes a neuronal calcium channel mRNA. Nature Neurosci. **2**, 785-790.

- Zou, A., **Lin, Z.**, Humble M.,, Creech C. D., Wagoner, P. K., Krafte, D., Jeglar, J., Wickenden, D. (2003). Distribution and functional properties of human KCNH8 (Elk1) potassium channels. Am J Physiol. Cell Physiol. **285** C1356-C1366.